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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,636	11/02/2001	Zheng Xin Dong	00537-186002	4976

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,636	DONG, ZHENG XIN	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of a preliminary amendment (filed 7/23/03), claims 1-9 and 15-18 have been cancelled, and claims 10-14 amended. Claims 10-14 remain pending.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

On pages 14-15, a procedure is given for assessing the propensity of a compound to displace (^{125}I) GLP-1(7-36) from RIN 5F rat insulinoma cells expressing the GLP-1 receptor. However, no result was given for this assay, and so there is no basis for concluding that the peptide of SEQ ID NO: 2 exhibits any capacity to bind to the GLP-1 receptor. It may well be the case that other analogs of GLP-1 bind to the GLP-1 receptor, but structure/activity relationships are unpredictable; i.e., one cannot predict GLP receptor binding merely by viewing the structure of a compound. Accordingly, "undue experimentation" would be required to use the compound of claim 10 to displace (^{125}I) GLP-1(7-36) from RIN 5F rat insulinoma cells expressing the GLP-1 receptor.

In the event that data is provided which shows the skilled biochemist how to use the compound of claim 10 to displace (^{125}I) GLP-1(7-36) from RIN 5F rat insulinoma cells expressing the GLP-1 receptor, claims 11-14 will remain rejected. Claim 11 is drawn to a "pharmaceutical" composition; as such, there is an implied assertion that the compound of claim 10 will be therapeutically effective to treat any of the recited diseases (diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorders, arthritis, osteoporosis, CNS disease, restenosis, neurodegenerative disease). However, there is no direction or guidance which would show the skilled endocrinologist or physiologist how to use the compound of claim 10 to treat any of these disorders. In addition, claim 10 recites the phrase "effective amount". Even if the term "pharmaceutical" were deleted from claim 11, the phrase "effective amount" would remain; as such, claim 10 would still assert therapeutic efficacy. In a similar vein, claim 12 is drawn to a method of eliciting an "agonist effect". This could potentially be construed as encompassing a method of eliciting an effect that will result in amelioration of symptoms of a disease. Again, there is no guidance, or evidence that shows the skilled artisan how to accomplish such a feat. Further, there is no indication or even an assertion as to what biochemical processes (e.g., cAMP production) might be altered as a result of contacting a cell with the claimed compound.

As indicated, even if in vitro data on the compound of claim 10 were provided, the reality

in pharmacology is that *in vitro* data that shows receptor antagonism or receptor stimulation is not predictive of therapeutic efficacy, or even, necessarily, of *in vivo* activity. As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) **55** (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional

determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) **2** (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

In accordance with the foregoing, it is clear that whether one is endeavoring to stimulate a receptor *in vitro* or to antagonize a receptor *in vitro*, extrapolating to a therapeutic method leads to "unpredictable" results.

Consider next the matter of endeavoring to treat an ill patient afflicted with diabetes. Each of the following references teaches "failure" in the treatment of diabetes:

- Nasushita R., "A case of acromegaly accompanied by adrenal preclinical Cushing's syndrome" (*Endocrine Journal* **46** (1) 133-7, 1999);

- O'Keefe J H Jr, "Improving the adverse cardiovascular prognosis of type 2 diabetes" (*Mayo Clinic Oroceedings* **74** (2) 171-80, 1999).

- Warner D P "Mortality and diabetes from a population based register in

Yorkshire 1978-93" *Archives of Disease in Childhood* 78 (5) 435-8, 1998)

- Maruyama Y, "A case of insulin dependent diabetes mellitus following systemic treatment for Vogt-Koyanagi-Harada syndrome" (*Ophthalmic Surgery and Lasers*, **31** (6) 487-90, 2000)

- Wandell P E "Drug prescription in diabetic patients in Stockholm in 1992 and 1995 - - change over time" (*European Journal of Clinical Pharmacology* **52** (4) 249-54, 1997)

- Mak K. H., "Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries" (*Journal of the American College of Cardiology* **30** (1) 171-9., 1997)

- Zuanetti G., "Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study" (*Journal of the American College of Cardiology* **22** (7) 1788-94, 1993).

As for treatment of obesity, the following are reviews on the subject: Kordik (*J. Med. Chem.* **42**, 181-201, 1999); and Bray (*Endocrine Reviews* **20**, 805-875, 1999). Between the two of them, there are considerable numbers of examples of "failure". Accordingly, "undue experimentation" would be required to practice the invention of claims 10-14. It is suggested that (a) data be provided which demonstrates that the compound of claim 10 can bind to the GLP-1 receptor, (b) the term "pharmaceutical" be deleted from claim 11, (c) the term "effective amount" be deleted from claim 11, and (d) that claims 12-14 be cancelled.

✧

Claims 11-13 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 11 recites an "effective amount" of a compound, but does not recite any objective of the efficacy. Accordingly, the claim is indefinite as to objectives.

- Claim 12 is drawn to a method of eliciting an "agonist effect". This claim is indefinite as to the manifestations of the agonist effect. Suppose that there are two rats, and one is given a compound of claim 10, and the other is given "vehicle" only. If the two rats were determined to be identical by a series of biochemical and physiological tests, would applicants argue that an "agonist effect" had been realized?

- Claim 13 recites the term "metabolic disorder". This renders the claim indefinite as to the disease(s) which may be encompassed.

- Claim 13 is indefinite as to the manifestations of a successful treatment. For example, suppose that the compound of claim 10 were administered to a human subject suffering from Alzheimer's Disease, and that as a result of the administration, there was a measurable change in serum glucose. Would this be considered a successful treatment?

Applicants are advised that the specification will be amended on pages 17-18 to reflect the maturation of applications 08/929363 and 08/740778 into USP 5,821,221 and 5,916,883, respectively, and that the specification will be amended (pp. 17-18) to reflect the the abandoned status of applications 09/015394, 09/121653, 09/131472 and 09/184413.

Reference "AV" was stricken from the IDS because it was not received, and is not present in parent application 09/206,601.

. . .

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600